IN THE UNITED STATES DISTRICT COURT

FOR THE SOUTHERN DISTRICT OF WEST VIRGINIA

THE CITY OF HUNTINGTON, Plaintiff, v. AMERISOURCEBERGEN DRUG CORPORATION, *et al.* Defendants.	Civil Action No. 3:17-01362
CABELL COUNTY COMMISSION, Plaintiff, v. AMERISOURCEBERGEN DRUG CORPORATION, *et al.* Defendants.	Civil Action No. 3:17-01665

EXPERT REPORT BY TRICIA WRIGHT MD, MS, FACOG, DFASAM

I am a medical doctor board certified in both Obstetrics and Gynecology, and in Addiction Medicine. I am currently Professor of Clinical Medicine at the University of California, San Francisco (UCSF). I relocated to California from Hawai'i in 2019 where I was an Associate Professor of Obstetrics and Gynecology and a Clinical Associate Professor of Psychiatry at the University of Hawai'i. In terms of education, I earned my Bachelor of Science Degree in Biological Sciences from Stanford University, my Medical Degree from the University of Michigan Medical School, and a Master's Degree in Clinical Research and Biomedical Sciences at the University of Hawai'i. A copy of my curriculum vitae is attached as Exhibit A to this report.

During my time in Hawai'i, I obtained state funding in 2006 to establish a clinic specializing in the care of pregnant and parenting women with substance use disorders (SUDs). I established the Perinatal Addiction Treatment (PATH) Clinic in 2007, serving as its Medical Director until May of 2011. I then

became the Women's Health Liaison with the Waikiki Health Center, a federally qualified health center, after it became a satellite clinic in that highly-respected health system. The PATH Clinic has won numerous local and national awards for providing compassionate and integrated care to this diverse group of patients. Throughout the course of my clinical practice, I have diagnosed, treated, counseled, and cared for thousands of pregnant and parenting women with substance use disorders, including opioid use disorder. In addition, my care and treatment of these women has extended to years postpartum. Because of my continued involvement with the mothers, I have been privileged to see their children grow and develop; many of whom experienced neonatal substance withdrawal following birth (also known as neonatal abstinence syndrome (NAS) or neonatal opioid withdrawal syndrome (NOWS)) and thrive today as their mothers remain sober and parenting.

Since moving to California, I have been working to improve screening and treatment of addicted women in the UCSF hospital system. Addiction affects every patient population; the more privileged are just able to hide it better because they often do not suffer the immediate consequences of loss of housing, employment, and other social and legal repercussions. To this end, I applied for funding to start alcohol screening and brief intervention in the faculty and resident practice population in order to prevent alcohol-exposed pregnancies and the long-term medical complications of alcohol use, arguably the most harmful drug in our society today. In addition, I work closely with the Addiction Medicine community at Zuckerberg San Francisco General Hospital (ZSFGH), where I work on the Addiction Medicine Consult service. I am also working to start a consult service and follow-up bridge clinic for women delivering at the UCSF-Mission Bay campus.

In addition to women with substance use disorders, I have also treated women with chronic pain during pregnancy, which often has included the appropriate prescribing and use of opioids. As a matter of course, I have counseled women on the effects of opioids on pregnancy, the need for treatment with medication as addiction treatment (MAT), as well as the incidence, prevention, and treatment of neonatal withdrawal. For many years, my partners and I at the University of Hawai'i delivered the babies and cared for their mothers in the hospital after delivery. It is important for the mothers to understand NAS and, if it occurs, for them to play an active role in the support and care of their babies through the withdrawal process. Since there were only a few buprenorphine treatment providers in Honolulu at that time, I continued treatment of these women for several years postpartum and had first-hand experience seeing the children of these women in the clinic grow up, since they would bring the children with them to their clinic visits, as well as for well-child care with the clinic pediatric provider.

In addition to my clinical experience, my research and professional activities have focused on the care of women with substance use disorders. I have held a waiver to prescribe buprenorphine since 2009, and teach buprenorphine waiver classes throughout the country. I was one of the developers of the joint educational program on buprenorphine-prescribing in pregnant women sanctioned by the American Society of Addiction Medicine (ASAM) and the American College of Obstetrics and Gynecology (ACOG). I have published over 25 papers on substance use disorders in pregnancy and edited the book "Opioid Use Disorders in Pregnancy: Management Guidelines to Improve Outcomes" that was published in 2018 by Cambridge University Press. I also authored several chapters in that textbook. I currently am chair of the Opioid and Addiction Medicine workforce and a member of the Fetal Alcohol Syndrome Champions

Taskforce at ACOG. I am the former chair of the Women and Substance Use Disorders Work Group for ASAM, and remain active in that organization.

The opinions offered in this report are based on my education, training, research, clinical experience, activities in professional organizations, and knowledge of the peer-reviewed medical and scientific literature in my areas of practice. My opinions are held to a reasonable degree of medical and scientific certainty.

Dr. Loudin's Report and Opinions Oversimplify A Complex And Multi-Factorial Problem (Addiction) That Has Plagued This Country For Decades.

I have reviewed the report submitted by Dr. Sean Loudin dated August 3, 2020. My opinions regarding neonatal abstinence syndrome, opioid and substance use, misuse and abuse by pregnant women, and the multitude of factors that impact babies born to addicted mothers are set forth below. However, as a preliminary matter, there are a number of fundamental observations and opinions that I offer directly in response to Dr. Loudin's report.

While Dr. Loudin's report and opinions purport to be about the specific impact of opioids in Huntington and Cabell County, in fact the data and studies that he cites are largely more properly characterized as being about the impact of "substances" or "drugs," including illicit substances and drugs. Women, including pregnant women, can and do use and misuse a variety of substances for a variety of reasons. Opioids hold no exclusivity in terms of the harmful effects of substance use on women and babies born to them. This is true across the country, as well as in West Virginia. I disagree with Dr. Loudin's opinions that single out opioids as the singular or primary cause of any person's addiction or substance use and misuse, much less the singular or primary cause of an entire county or state's public health crisis. Based on my experience and expertise in the area of addiction and obstetrics, it is my opinion that the circumstances under which a woman uses opioids during pregnancy (sometimes resulting in the birth of a baby with NAS) is invariably multifactorial, with unique beginnings and most often involve the use of more than one neurotoxic substance. Not all addiction problems start with a prescription opioid, not all addictions evolve from opioid use, and not all babies diagnosed with NAS have been exposed to opioids. To the contrary, in my experience, most NAS babies have been exposed to a variety of neurotoxic substances. Indeed, Dr. Loudin's report acknowledges as much: the West Virginia Perinatal Partnership definition he cites for NAS is in part that it is diagnosed "when a baby has intrauterine exposure to **a neuroactive substance**" (Loudin Report at 6 (emphasis added)).

Second, Dr. Loudin's references to data and inclusion of graphs underscore the fact that polysubstance use is the rule, not the exception. Most of the data and graphs to which he refers pertain to drug use or substance use generally. When there are data or references to opioids specifically, it should be noted that such data are mixed in with data about other substances. In addition, much of the data confirms the relevance of the use of non-opioid substances, whether exclusively or in polysubstance use alongside opioids. For example, in paragraph 38 and Figure 4 of his report, Dr. Loudin relies on a 2009 umbilical cord study initiated with funding from the West Virginia Department of Health and Human Resources, Bureau of Public Health, Office of Maternal, Child and Family Health, with federal Maternal and Child Health Block Grants. The results of the study showed that a number of substances, not just opioids, were

found in the cord tissue - 40% marijuana, 27% alcohol, and 12% benzodiazepines. This study highlighted the fact that at that time almost 1 in 5 babies born in those six hospitals in West Virginia were exposed to ***drugs*** *in utero*. This was one of the prompts for the state to "focus on substance use and addiction during pregnancy," not just opioid use.

Finally, it is not correct to say that opioid use is responsible for causing polysubstance use or for causing all downstream health problems associated with drug addiction. The problems faced by pregnant women and their babies cannot be traced solely to opioids and their challenges are not simple or linear. This country has faced addiction epidemics for decades and, although certain types of substances might get more specific focus at times (e.g., cocaine, crack, meth, alcohol, opioids….), experience tells us that addiction involves a multitude of factors that go far beyond the availability or use of a particular substance.

NAS Is A Heterogeneous And Short-Term Condition

Neonatal abstinence syndrome (NAS) is an umbrella term for the symptoms newborn infants experience from being exposed *in utero* to any number of substances, including opioids, benzodiazepines, nicotine, antidepressants, and other prescribed and non-prescribed substances. The acronym NOWS (neonatal opioid withdrawal syndrome) is used to mean withdrawal from opioids specifically. As the majority of affected infants are exposed to more than one substance, NAS is a more accurate term for the purposes of this report. The symptoms of NAS are multitude and depend on many factors including the timing and amount of exposure, the half-life of the drugs ingested, other drugs taken, the gestational age at birth, genetic risk, gender of the infant, and even the protocols of the treating hospital.

Generally, the term NAS refers to a temporary and treatable condition with symptoms including gastrointestinal (GI) upset, high-pitched cry, feeding difficulties, inconsolability, and sleeping difficulties. The risk of developing NAS is not universal, as only approximately 60% of infants exposed to opioids *in utero* develop any symptoms of NAS and, in experienced hands, less than 20% require treatment. In other words, *in utero* exposure to opioids does not always cause NAS (and certainly, opioid use by the mother before pregnancy cannot cause NAS). The diagnosis of NAS is highly subjective, as it requires observation of physical symptoms that can mimic other medical conditions. Many studies have shown that when observers are not blinded to exposure status, they give a higher score to babies with opioid exposure on things like irritability, crying, sleeping, and ability to feed. As the majority of babies with opioid exposure are treated in the newborn ICU, and thus separated from mom, many of these symptoms of NAS are really maternal abstinence syndrome – in that they reflect the babies' reaction to separation from their mothers – and not necessarily NAS symptoms. Studies on rooming-in protocols have consistently shown that keeping mom and baby together, encouraging breast feeding, and not treating babies in the loud and bright NICU setting, improve outcomes and decrease the need for medical treatment.

NAS is generally considered a temporary and treatable event. Studies done on infants affected by prenatal opioid exposure have generally not shown serious long-term effects when controlled for other exposures, especially alcohol and tobacco, poverty, diet, interpersonal violence, and access to early interventional care. The best outcomes often occur in families that are able to stay intact and with

mothers that are able to maintain treatment with MAT long-term. But these outcomes depend heavily on a variety of factors, including the mother's course with regard to treatment, the family situation, foster or adoption options, as well as the resources and policies available in the community. Not every community has specialized evidenced-based treatment facilities, or even providers who can prescribe MAT.

NAS is a highly heterogeneous condition; it differs by the type of substances used by the mother during pregnancy, and it differs in its presentation and its treatments. Its incidence is highly dependent on the type of substance use, the timing of exposure, the genetic susceptibility, and even the hospital where NAS is diagnosed and treated. The mothers using opioids and other substances differ in almost all variables. They come from every age group, ethnicity, socio-economic class, sexual orientation, and even gender identification; thus, exposure assessment, risk of NAS, diagnosis of NAS, and the need for and type of treatment must be individualized.

Women Who Use Opioids And Other Substances During Pregnancy Are A Diverse Group

Over the course of my career, I have treated thousands of pregnant women with substance use disorders and have worked with hundreds of other healthcare providers who also serve these women and their babies. This group of women is very diverse. They differ in age, ethnicity, religion, geographic residency and history, education level, socioeconomic status, family support, medical history, genetic susceptibility to addiction or substance use disorder, co-morbid conditions and health status, etc. The care and treatment of such women is highly individualized. These diverse variables also affect differentially the impact on the degree of prenatal care they have or do receive, the degree of high-risk behavior they engage in, as well as their compliance with treatment and healthcare recommendations.

The majority of women who use opioids during pregnancy have polysubstance use or misuse, meaning they use and/or misuse a number of different substances during their pregnancy. Such substances can be prescribed, legal or illicit, and are wide-ranging in type. They include but are not limited to alcohol, tobacco, methamphetamines, cannabis, cocaine, benzodiazepines, SSRIs, and opioids. Polysubstance use and polypharmacy is the rule, not the exception. This reality makes the assessment of substance use risk to the mother and the fetus quite variable. The type of substance used (prescribed or otherwise), when in the pregnancy the substance was used, the dose and duration of use of the substance, and the reason for the medication use (if prescribed), all will result in different effects on the mother and the fetus

The women who use opioids during pregnancy (and thus may have infants with neonatal withdrawal) use opioids for a variety of reasons. Some may be illicit, but many are for legitimate reasons, including those being treated with opioids for acute and chronic pain, those with an opioid use disorder prescribed opioid agonist therapy (such as methadone or buprenorphine), and those with an untreated opioid use disorder. The clinical and social characteristics of these women vary widely, in that they come from all ethnic groups and socioeconomic classes, and have a wide range of social supports. Each of these characteristics impacts the risk of the infant developing neonatal withdrawal or NAS. For example, the women being treated with opioids for acute or chronic pain generally are on lower doses of opioids, have greater access to clinical care, are more likely to be getting prenatal care, and generally have better social supports. For these reasons, they generally have less risk of being reported to child welfare, and

less overall social stress. All of these factors influence the risk that their baby will be born with NAS, and some data indicate that they are much less likely to have an infant diagnosed with NAS. On the other hand, some of the other medications used to treat chronic pain such as antidepressants, benzodiazepines, muscle relaxants, and anti-seizure medications may increase the risk that the infant develops withdrawal symptoms. The concurrent use of any other substance, illicit or prescribed, will increase the risk of NAS in the baby, irrespective of the use of prescribed opioids.

Women who are prescribed opioids for acute and even chronic pain (while pregnant or otherwise), and who do not have another substance use disorder (including tobacco), will have a low risk of developing an opioid use disorder. One study showed that for women who had a cesarean section and were prescribed opioids, the risk of developing an opioid use disorder is approximately 1/300. The narrative that all people who are prescribed opioids go on to develop an opioid use disorder is false. In addition, a great majority of the patients I treat with an opioid use disorder say their first substance was not prescribed opioids, but rather it was tobacco or alcohol. In other words, the appropriateness of the prescribing, use, risk/benefit analysis, and subsequent substance use or abuse involves innumerable factors that are different for every physician and every woman.

Women are often treated with opioids for acute and chronic pain during pregnancy because there are no alternatives or few safe alternatives. Non-steroidal anti-inflammatories (NSAIDS), such as ibuprofen, naproxen, and aspirin, are not recommended during pregnancy. This often leaves opioids as the only option to treat pain during pregnancy. Leaving pain untreated is not a safe option; exposure to untreated pain increases cortisol levels and can be harmful to the developing fetus. As ACOG guidelines state: Pregnancy should not be a reason to avoid treating acute pain because of a concern for opioid misuse or NAS. For chronic pain in pregnant women, the practice is to avoid or minimize use of opioids – but they can be used subject to the physician's discretion and with caution after trying non-pharmacologic treatments. These practice guidelines apply to pregnant women irrespective of whether they are also using other substances. The timing of treatment can range from treatment after surgery in the first trimester to the treatment of acute back pain close to term. Only infants who are exposed to opioids around the time of birth are at risk of developing NAS.

There are also enormous differences between the healthcare providers and the facilities in which these women get care. Different physicians have different approaches to opioid use during pregnancy. Level of experience and degree of expertise in addiction will influence prescribing and treatment decisions. Different hospitals have different drugs and treatment modalities available. Insurance and cost often impact drug and treatment availability and preferences. All of these differences affect the pregnant woman and their baby's risk of NAS.

Women being treated for opioid use disorder (OUD) with methadone or buprenorphine also come from a wide range of ages, ethnicities, geographic regions, educational backgrounds, and socioeconomic statuses. They may also have a different genetic susceptibility to developing a substance use disorder, and thus pass on some of that genetic susceptibility to their children. They are more likely to smoke cigarettes and use other substances such as alcohol and stimulants, which increases the chance of an infant being born with NAS as compared to women who only use prescribed opioids. Geography makes a difference as well. Depending on where they live, the pregnant person may have access to one medication and not the other. Indeed, it has been shown that treatment with buprenorphine results in

less severe NAS than treatment with methadone, but access to buprenorphine treatment is not available in all areas. In many areas, neither treatment is available, leaving the woman vulnerable to continued illicit opioid use and self-substitution with alcohol, which is by far the most dangerous substance used in pregnancy.

Drinking during pregnancy directly causes fetal alcohol syndrome, the most common cause of birth defects and developmental delay in children. Current reports estimate that up to 5% of children born in this country suffer from fetal alcohol spectrum disorders (the same prevalence as autism spectrum disorders). Despite these known harms, alcohol use during pregnancy remains common. The most recent data show that 53% of women report alcohol use in the past month, and of those, 11.5% also reported pregnancy (NSDUH 2017). Among women who use opioids during pregnancy, both prescribed and non-prescribed, these numbers are higher. Aggregate data from the 2005 to 2014 NSDUH show that, among pregnant women who report using opioids non-medically, 48% reported alcohol use during pregnancy and 32% report heavy or binge use in the past month. This heavy and binge use is causally linked to fetal alcohol syndrome, a permanent and debilitating medical condition. This relationship of OUD in pregnancy to alcohol use has received little attention, and is likely related to many of the long-term developmental issues found in poly-substance exposed infants. Alcohol use during pregnancy is not routinely screened for and is more difficult, in large part because of the short half-life of alcohol.

Another cause of developmental disability is direct exposure to tobacco smoke *in utero*. Fetal exposure to tobacco smoke is extremely common for infants exposed to opioids. Among women with an OUD during pregnancy, up to 97% also use tobacco. These numbers are less among women who use opioids for acute and chronic pain. Smoking during pregnancy increases the risk of serious pregnancy complications, such as preterm delivery, preterm or premature rupture of membranes, placental separation, and miscarriage. The exposed fetus and infant have increased rates of low birth weight, prematurity, sudden infant death syndrome, and childhood respiratory illnesses, such as asthma. Heavy smoking during pregnancy also worsens NAS symptoms in infants exposed to opioids and tobacco.

The pregnant woman with an untreated opioid use disorder has the highest risk of pregnancy complications. This includes continuing cycles of withdrawal, which stress the fetal brain and increase the risk of preterm birth and other pregnancy complications. For these reasons, as well as vastly decreased mortality rates, treatment with methadone or buprenorphine is recommended as the treatment of choice by all major medical groups including the American College of Obstetricians and Gynecologists (ACOG), the American Society of Addiction Medicine (ASAM), and the American Academy of Pediatrics (AAP), despite the risk of the infant developing NAS. People with opioid use disorders come from all ages, ethnicities, education levels, and socioeconomic statuses. These and other factors influence the care they receive, and thus influence the risk of pregnancy complications. For example, a well-educated woman who injects heroin in the privacy of her own house will be at a much lower risk of incarceration and will, therefore, be at a lower risk of forced withdrawal and pregnancy complications, as compared to a woman forced by homelessness and poverty to inject on the streets, who will be at a greater risk of forced withdrawal and pregnancy complications. The well-educated woman will also often have more access to prenatal and other medical care, which has been shown to ameliorate the complications of substance use during pregnancy.

Babies With NAS, Their Treatment and Its Impact On Them, Differ In A Multitude of Ways

Just as women who use opioids differ in almost all respects, their infants also differ. Because NAS is a drug withdrawal syndrome, the presentation for each infant differs depending on which drugs they were exposed to, when they were exposed, the indication for the exposure, the other medical conditions the infants might have, the gestational age at which they were born, the ability of the mom to care for the infant, the protocols for diagnosis at the hospital where they are being treated, and the treatment given for NAS.

The timing of drug exposure is critical. For example, opioid exposure during the first trimester does not cause the infant to develop NAS, nor does acute opioid exposure at the time of childbirth. Only chronic exposure during the final part of the pregnancy can cause opioid-related NAS (or NOWS). If a woman takes opioids only during her first trimester, for example, but then takes benzodiazepines during the final portion of her pregnancy, any NAS symptoms shown by the infant would be related to the benzodiazepines, not the opioids. Similarly, any discussion of birth defects in babies exposed to opioids *in utero* must take into account the timing of exposure. The great majority of studies looking at the relationship with opioid exposure and birth defects have found no association with NAS or opioid exposure. As birth defects only develop from exposure during specific time periods depending on the organ system involved, which is almost entirely during the first trimester of pregnancy, opioid exposure would have to happen during that window for there to be any possible connection to a birth defect. Notably, this is not the time at which opioid exposure can cause NAS, which is the end of the pregnancy. There is no direct connection between NAS and birth defects. Moreover, the great majority of studies looking at the relationship between opioid exposure and birth defects have found no association and those that do find an association did not control for the reasons the women took the opioids (for example, the woman undergoing surgery in the first trimester for an appendicitis who is also exposed to the stress effects of the surgery, the inflammation from the inflamed appendix, and other medications such as anesthetic agents given during that time).

The infants with NAS also differ in the types of opioids to which they are exposed. Just as women use different types of opioids depending on the indication, the infants are exposed to these different opioids. Different opioids have different effects and different half-lives. Buprenorphine is a partial opioid agonist, meaning it has a muted effect on the *mu*-opioid receptor. It sits on that receptor and binds tightly, but does not fully activate that receptor. For this reason, buprenorphine does not cause the feelings of euphoria or cause the respiratory depression that full agonists such as heroin or methadone do. Buprenorphine has been shown to cause less severe NAS than methadone, likely because of these different molecular effects. A medication's half-life (how long it takes for half of the effects to wear off) differs by medication. Methadone and buprenorphine have very long half-lives, which means that the effects wear off very slowly, making them more ideal to treat addiction. These different half-lives also influence the incidence and treatment of NAS, as these medications are used to treat NAS. Medications also differ in their ability to cross the placenta and get into the fetal circulation. These differences are also influenced by the genetics of the mother and the infant.

The presentation of NAS is extremely variable in symptoms and duration. The majority of infants display symptoms within the first 72 hours of life. These symptoms can range from mild irritability to extreme difficulties with feeding, sleeping, and being consoled. If not treated, these symptoms can be severe and

occasionally life-threatening. Because of the variability of the symptoms and the largely unfounded fear of severe consequences, the majority of infants in this country have traditionally been over-treated, usually in the neonatal intensive care units, which is expensive, and in most cases, unnecessary and counterproductive. More recently, the protocols for hospitals have been changing, leading to a lot fewer infants requiring treatment. These new protocols rely on keeping mothers and infants together, which require a mom be healthy enough to care for the infant, and thus being treated for her own medical condition, either the chronic pain or the opioid use disorder.

As mentioned earlier, the scoring systems and decision to treat the infant for NAS is highly subjective. For hospitals lacking a clear protocol for treatment, which in this country are the majority of hospitals, the outcomes are worse, the length of stay longer, and the costs are higher. Babies are often over-scored and over-treated. I took care of one mom treated with oxycodone for back pain in pregnancy, whose son was erroneously scored in the treatment range, received too much morphine, and thus had a lengthy hospital stay while withdrawing from that initial treatment. His two sisters were not diagnosed with NAS, were treated appropriately and had normal hospital stays.

Again, the worst outcomes are for the infants of moms with untreated opioid use disorder who were not only exposed to varying ranges of opioids during pregnancy, but often to many other drugs (both licit and illicit), infectious diseases, poor diet and psychosocial stress. These babies are born stressed out and often premature, and their mothers, because they did not receive care and are likely still suffering from the effects of their own SUD, are less likely to be able to care for these infants in the hospital and at home. Instead of focusing on just the opioids, our society needs to focus on providing quality addiction care for all women and all substances (including alcohol, tobacco, benzos, etc.) before, during, and after pregnancy. If the women do not get treatment for their addiction during pregnancy, the outcomes for the infants are much worse than any of those caused by NAS.

A diagnosis of NAS does not always signify the baby's withdrawal from opioids. In the past 10-15 years, it has become standard of care to screen babies for NAS if the mother tests positive for opioids when they come to the hospital in labor or self-report that they have taken opioids in one form or another (e.g. asking for dose, mention maintenance therapy during history, etc.). The Finnegan scale and other scales used to evaluate potential NAS measure subjective clinical signs that are non-specific to opioid exposure or withdrawal. Babies can exhibit such signs for any variety of reasons, including nicotine withdrawal (90% of mothers in MOTHER study were also smoking cigarettes), benzodiazepine exposure, anxiety medication exposure, depression medication exposure, and even untreated maternal depression (thought to be related to cortisol in baby's system). The fact that some treatment with opioids eases symptoms also does not necessarily connect the dots because opioids relieve pain and discomfort which, not surprisingly, reduces irritability and other NAS-like symptoms. So a diagnosis of NAS does NOT necessarily equate to significant opioid exposure and withdrawal, and treatment does not necessarily reveal that either. Many babies with a NAS diagnosis do not receive opioid treatment and it would require an individualized assessment to determine whether a NAS baby's treatment suggested that opioids were the sole or substantial cause or not.

The long-term studies of children with a history of NAS often group all of these children into "NAS exposed." Groups resulting from such a population definition are often heterogeneous amalgams of children who have either been known to be opioid-exposed and/or experienced withdrawal symptoms at

birth, sometimes based on Diagnostic and Statistical Manual/International Statistical Classification of Diseases and Related Health Problems-9/10 codes (ICD). The scientific rigor of this definition is questionable. It is unclear from the studies whether the group actually represents all children prenatally exposed to opioids. They do not specify the types of opioids, the exposure length, the amount of exposure, the indication for exposure, and whether or not the infant actually was treated for NAS. As a clinician, I am extremely leery of any study that relies on ICD9/10 codes, as they are notoriously incomplete and often inaccurate. Moreover, ICD9/10 codes are not specific to *opioid*-related NAS. The codes can include any type of withdrawal symptom at birth, including withdrawal from other prescribed or illicit drugs. In addition, the comparison groups are often not chosen thoughtfully. For there to be a meaningful comparison, the groups would need to be similar in all aspects except for the exposure to opioids. These studies often just choose infants that are born at the same hospital around the same time. They do not control for the effects of poverty, maternal stress, poor diet, alcohol, tobacco use, and the course of prenatal care.

The studies that show that NAS is associated with poor development are likely to fall prey to the single-cause fallacy—developmental delay is related to opioid exposure which is related to NAS, so, implicitly, NAS causes developmental delay. Controlled data indicate that most children who have experienced NAS likely will grow up during their first 3 years of life within normal developmental limits. Finally, to the extent there are developmental differences between children with and without a NAS diagnosis, such differences are likely due to any one or more causes (directly or indirectly: parental mood disorders, trauma history, polysubstance use, parenting practices, inadequate nutrition, health care access, and other social determinants of health. The studies referenced here are listed below.

The MOTHER study is a randomized controlled trial (RCT) of 175 women who had OUD during pregnancy. They were randomized to either receive methadone or buprenorphine. The group of infants whose mothers received buprenorphine required much less morphine for treatment of NAS and spent much less time in the hospital. Being an RCT, the authors controlled for other exposures. The only other substance these infants were exposed to was tobacco, as 97% of the women in the study smoked cigarettes. The two groups have been studied longitudinally and the infants have shown no significant differences in long-term development from each other and no significant developmental disabilities overall. This negates the hypothesis that exposure to opioids causes long-term developmental harm in the children of women being treated for opioid use disorder.

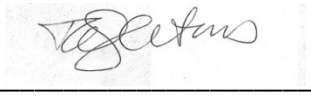
Any alarmist tone prevailing today harkens back to the “crack baby epidemic” of the 1980s. This alarmist tone in the media served to stigmatize a generation of children who are now adults. Long-term studies of infants of mothers who used crack cocaine in the 1980s have shown minimal effects from the drug itself and major effects from the societal pressures that they faced. I currently work alongside such an exposed person. He is currently finishing his maternal-fetal medicine fellowship and starting on what is expected to be a long and fulfilling career of taking care of women with high-risk pregnancies and their infants.

NAS was first described in 1875 in Germany and the diagnosis and treatment approaches have evolved over time. There have been opioid and other drug epidemics throughout history around the world, but the treatment of pregnant women with OUD with methadone became the standard of care in the 1950s and 1960s, and the screening and treatment of their children using the protocols developed by Loretta Finnegan were developed. We have now had over 50 years of experience caring for babies with NAS, and

we have had 50 years of studying these children. There are still no specific long-term syndromes or conditions that are recognized as being caused by NAS or opioid exposure. The majority of these children have gone on to live normal lives. The problems they have stem from the treatment of their mothers as criminals, the stigma they faced, and the poverty and poor situations in which they were raised.

I reserve the right to supplement this report and my opinions on the basis of new or later-acquired information and materials relevant to the matters addressed. I charge $400 per hour for my time in reviewing literature, medical records, conducting research, preparing reports and meeting with counsel. I charge $550 per hour for my time giving testimony in deposition or trial. Over the last four years, I have given testimony in one deposition in February of 2018 (Dominguez) in Honolulu, Hawaii.

Date: August 27, 2020



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Tricia Wright, MD, MS, FACOG, DFASAM

TRICIA WRIGHT, MD - MATERIALS CONSIDERED AND/OR RELIED UPON

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Expert Report of Sean Loudin, MD